Labeling Guidance
Revised May, 1992

METAPROTERNOL SULFATE INHALATION SOLUTION USP 5%

DESCRIPTION

Metaproterenol sulfate inhalation solution is a bronchodilator administered by oral inhalation via intermittent positive pressure breathing (IPPB) apparatus or nebulizer.

Metaproterenol sulfate is 3,5-dihydroxy- α-[(isopropylamino)methyl] benzyl alcohol sulfate, a white crystalline, racemic mixture of two optically active isomers. It differs from isoproterenol hydrochloride by having two hydroxyl groups attached at the meta positions on the benzene ring rather than one at the meta and one at the para position. It has the following structual formula:

$(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$ MW = 520.59

Contains metaproterenol sulfate 5% in a pH-adjusted aqueous solution. (*Note: Include the pH-range of the final solution.)* In addition, the following inactive ingredients are present:

[Include the names of all inactive ingredient per 21 CFR 201.100(b)(5)].

CLINICAL PHARMACOLOGY

Metaproterenol is a beta adrenergic agonist bronchodilator which has a rapid onset of action. The pharmacologic effects of beta adrenergic agonist drugs, including metaproterenol, are at least in part

attributable to stimulation through beta adrenergic receptors of intracellular adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'- adenosine monophosphate (c-AMP). Increased c-AMP levels are associated with

relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Absorption, biotransformation and excretion studies following administration by inhalation have not been performed. Following oral administration of tablet and solution, an average of 40% of the drug was excreted as the unchanged drug and its major metabolite, a polar conjugate, metaproterenol-O-sulfate.

Recent studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Following controlled single dose studies by an intermittent positive pressure breathing apparatus (IPPB) and by hand-bulb nebulizers, significant improvement (15% or greater increase in FEV_1) occurred within 5 to 30 minutes and persisted for periods varying from 2 to 6 hours. The longer duration of effect occurred in the studies in which the drug was administered by IPPB, i.e., 6 hours, versus 2 to 3 hours when administered by hand-bulb nebulizer. The doses used were 0.3 mL by IPPB and 10 inhalations by hand-bulb nebulizer.

In controlled repetitive dosing studies by IPPB and by hand-bulb nebulizer the onset of effect occurred within 5 to 30 minutes and duration ranged from 4 to 6 hours. The doses used were 0.3 mL b.i.d. or t.i.d. when given by IPPB, and 10 inhalations q.i.d. (no more often than q4h) when given by hand-bulb nebulizer. As in the single dose studies, effectiveness was measured as a sustained increase in FEV_1 of 15% or greater. In these repetitive dosing studies there was no apparent difference in duration between the two methods of delivery.

Clinical studies were conducted in which the effectiveness of metaproterenol sulfate was evaluated by comparison with that of isoproterenol hydrochloride over periods of two to three months. Both drugs continued to produce significant improvement in pulmonary function throughout this period of treatment.

INDICATIONS AND USAGE

Metaproterenol sulfate inhalation solution is indicated as a bronchodilator in the treatment of asthma and bronchitis or emphysema when a reversible component is present in adults.

CONTRAINDICATIONS

Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions and paradoxical bronchospasm can occur. Therefore, metaproterenol sulfate inhalation solution is contraindicated in patients with a history of hypersensivity to any of its components.

WARNINGS

Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of metaproterenol as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Controlled clinical studies and other clinical experience have shown that metaproterenol, like other inhaled beta adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. Paradoxical bronchospasm has been reported after the use of inhaled sympathomimetic drugs and may be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

PRECAUTIONS

General: Because metaproterenol is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, convulsive disorders, cardiac arrhythmias, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines. Significant changes in systolic and diastolic blood pressure and heart rate could be expected to occur in some patients after use of any beta adrenergic bronchodilator.

Physicians should recognize that a single dose of nebulized

metaproterenol sulfate in the treatment of acute asthma may alleviate symptoms and improve pulmonary function temporarily but fail to completely abort an attack.

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

Metaproterenol effects may last up to 6 hours or longer. It should not be used more often than recommended and the patient should not increase the number of inhalations or frequency of use without first consulting the physician. If symptoms of asthma get worse, adverse reactions occur, or the patient does not respond to the usual dose, the patient should be instructed to contact the physician immediately.

A single dose of nebulized metaproterenol in the treatment of an acute attack of asthma may not completely abort an attack.

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed.

Pregnancy: TERATOGENIC EFFECTS: Pregnancy Category C: Metaproterenol has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose; the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separtion. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg or 310 times the human inhalation dose. There are no adequate and well-controlled studies in pregnant women. Metaproterenol sulfate inhalation solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when metaproterenol sulfate is administered to a nursing woman.

Pediatric Use: See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Adverse reactions are similar to those noted with other sympathomimetic agents.

The following table summarizes the adverse experiences reported for at least 2% of the 120 patients participating in multiple-dose clinical trials of 60 and 90 day duration.

Adverse Experiences Occurring In At Least 2% of Patients in 60 And 90 Day Clinical Trials N=120

Adverse Experience	No. of Patients	%
Cough	4	3.3
Headache	4	3.3
Nervousness	17	14.1
Tachycardia	3	2.5
Tremor	3	2.5

It is important to recognize that adverse reactions from beta agonist bronchodilator solutions for nebulization may occur with the use of a new container of a product in patients who have previously tolerated that same product without adverse effect. There have been reports that indicate that such patients may subsequently tolerate replacement containers of the same product without adverse effect.

OVERDOSAGE

The symptoms with overdosage are those of excessive beta-adrenergic stimulation and those listed under ADVERSE REACTIONS. Treatment consists of discontinuation of metaproterenol sulfate together with appropriate symptomatic therapy.

DOSAGE AND ADMINISTRATION

The dosage and administration are summarized in the table below.

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Metaproterenol sulfate inhalation solution is administered by oral inhalation via IPPB or nebulizer.

Usually, treatment need not be repeated more often than every four hours to relieve acute attacks of bronchospasm. Metaproterenol sulfate inhalation solution may be administered three or four times a day for the treatment of reversible airways disease in adults. A single dose of nebulized metaproterenol sulfate in the treatment of an acute attack of asthma may not completely abort an attack.

As with all medications, the physician should begin therapy with the lowest effective dose and then titrate the dosage according to the individual patient's requirements.

POPULATION	METHOD OF ADMINIS-TRATION	USUAL SINGLE DOSE	RANGE	DILUTION
Adult	Hand-bulb nebulizer	10 inhalations	5 to 15 inhalations	No dilution
12 years and older	IPPB or nebulizer	0.3 mL	0.2 mL to 0.3 mL	Diluted in approx. 2.5 mL saline soln. or other diluent

HOW SUPPLIED

- Established name
- Dosage form and strength
- Packaging
- Special handling and storage conditions
- USP labeling requirements

Manufactured by statement
Date of latest revision